

**DERMATOLOGIC AND OPHTHALMIC DRUGS  
ADVISORY COMMITTEE BRIEFING DOCUMENT  
FOR  
NDA 21-177**

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## **ATTACHMENTS**

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## **1. OVERVIEW**

Patients with severe recalcitrant nodular acne have benefited from the use of Accutane® (isotretinoin) since it was first marketed in 1982. Severe recalcitrant nodular acne is a disfiguring disease that can often result in significant permanent scarring. Patients with severe recalcitrant nodular acne have failed topical and systemic antibiotic treatment and have few alternative effective therapeutic modalities other than Accutane.

- New micronized formulation with pharmacokinetic advantages

A new formulation of isotretinoin, Accutane NF, was developed and submitted as a New Drug Application (NDA 21-177) in October 1999. This micronized formulation has pharmacokinetic advantages over the current marketed Accutane, namely administration independent of food consumption and reduced variability in exposure. Thus, taking Accutane NF with or without food produces comparable exposures. In contrast, taking the current marketed Accutane with or without food markedly alters exposure levels (by a factor of 2), leading to the risk of suboptimal results [Colburn et al., 1983]. Accutane is prescribed for administration twice per day in divided doses and must be administered with food. Several steps will be taken to manage the risk of potential confusion between the new and old formulations of isotretinoin.

- Clinically equivalent efficacy with safety advantages

A large clinical trial (602 patients randomized to treatment) showed that Accutane NF has efficacy equivalent to Accutane with clinically relevant safety and tolerability advantages. No new safety concerns were observed in this trial. The new formulation of isotretinoin will be dosed once per day at 0.4 mg/kg with or without food. Four pharmacokinetic studies submitted as part of this NDA assessed the food effect on bioavailability; established the bioequivalence of clinical and registration lots of Accutane NF; and established the dose proportionality of three registration lots of Accutane NF. When considered together the results clearly indicate that the new formulation of isotretinoin, administered with or without food, will provide appropriate exposure to isotretinoin to produce clinically equivalent efficacy with safety advantages, when compared with Accutane administered with food.

## **2. ACCUTANE NF NDA**

- *Micronization of isotretinoin leads to administration independent of food consumption, reduced variability, and increased bioavailability*
- *The micronized formulation achieved clinically equivalent efficacy with clinically relevant safety and tolerability advantages and no new safety concerns.*

### **2.1 Clinical Program**

The clinical program consisted of: (a) a single clinical study, Protocol NR15645, in which 602 patients were randomized to either 0.4 mg/kg Accutane NF once daily without food or 1.0 mg/kg Accutane in two divided doses daily with food in a double-blind, parallel-group, multi-center design to demonstrate that these formulations were clinically equivalent; and (b) four

pharmacokinetic studies: to assess the food effect on bioavailability; to establish the bioequivalence of clinical and registration lots of Accutane NF; and to establish the dose proportionality of three registration lots of Accutane NF.

### **2.1.1 Design of the Pivotal Clinical Trial**

The pivotal clinical trial, NR15645, was a double-blind, randomized, parallel-group, multi-center study. The study design included a screening/baseline evaluation followed by randomization to receive either Accutane capsules, twice daily with food at a total dose of approximately 1.0 mg/kg, along with placebo capsule(s), or to receive Accutane NF, at a once daily total dose without food of approximately 0.4 mg/kg, along with placebo capsule(s), for a period of 20 weeks. The objective of the study was to demonstrate that Accutane NF when administered once daily at 0.4 mg/kg without food is as effective as Accutane administered twice daily at 1.0 mg/kg in divided doses with food.

The number of patients was selected to ensure sufficient power to establish an equivalence criterion of 25%, i.e., the 90% confidence interval on the ratio of the mean response (nodular lesion count from baseline) of Accutane NF to that of Accutane must be between 0.75 and 1.25. A total of 496 evaluable patients was required. Six hundred and fifty-seven patients were screened for enrollment at 17 centers, 602 of which were randomized to treatment.

### **2.1.2 Analysis of Efficacy Variables**

By agreement with the FDA, the 95% two-sided confidence interval of the ratio of least squares means of change of total nodular lesions from baseline at week 20 for Accutane NF and Accutane was calculated using Fieller's Theorem [Fleiss, 1981]. Consistent with the equivalence definition specified in the study protocol, if the 95% confidence interval of the ratio of the least squares mean of the change from baseline of Accutane NF to that of Accutane is between 0.866 and 1.118 then the equivalence of the clinical efficacy was concluded. This range represents 0.75-1.25 on the square root transformed scale.

### **2.1.3 Demographics**

The treatment groups were comparable with respect to age, gender, race, weight, and height. The mean age was  $22.2 \pm 8.2$  years in the Accutane NF group and  $21.2 \pm 6.5$  years in the Accutane group. Approximately 67% of patients in the Accutane NF group and 61% in the Accutane group were male. Approximately 80% of patients in each treatment group were Caucasian with the other 20% of patients distributed among Black, Oriental, Hispanic, and other racial categories. There were no significant differences between the two treatment groups in terms of mean weight or height. Overall, the patients enrolled in the study reflect the age and gender distribution of the population with this disease.

## 2.2 Efficacy

### 2.2.1 Summary of Clinical Results

- *There were no statistically significant differences between the two treatment groups in nodule counts at baseline*
- *The two formulations were equivalent in terms of the change from baseline at Week 20 in the total number of nodules*
- *The two formulations were equivalent in terms of the proportion of patients who achieved at least a 90% reduction in total nodules from baseline at Week 20*

### 2.2.2 Baseline Nodule Count

The mean number of nodules, including both facial and truncal nodules, was  $20.6 \pm 18.4$  (range 10-200) in the Accutane NF group and  $18.7 \pm 13.1$  (range 10-111) in the Accutane group. For enrollment in the study, the minimum requirement was 10 nodules. The mean number of nodules observed at baseline in both groups is approximately twice this value, which attests to the severity of acne studied in this trial.

### 2.2.3 Change in Nodule Count from Baseline at Week 20

The data in Table 1, which is based on the per protocol population, show that facial nodule counts were reduced by 91.4% and 93.5% for patients in the Accutane NF and Accutane groups, respectively. Similarly, truncal nodule counts were reduced by 84.3% and 88.3% for patients in the Accutane NF and Accutane groups, respectively. The decrease from baseline at Week 20 is therefore greater for facial nodules than for truncal nodules. Total nodule counts decreased 88.8% for patients in the Accutane NF group compared to 90.4% for patients in the Accutane group.

The 95% confidence intervals for ratios of changes in these variables (facial, truncal, and total nodules) fall within the interval of 0.866 to 1.118, which is required for equivalence (Table 1).

An analysis was also performed on the change from baseline in total nodules for patients whose last assessment was between Week 16 and Week 20. This population most closely matched patients at the end of current Accutane therapy. Nodule counts were reduced by 89.3% and 90.9% for patients in the Accutane NF and Accutane groups, respectively. The analysis for the per protocol population yielded a confidence interval of 0.894 to 1.003, which meets the criterion for equivalence.



**Table 1**      **Change in Total Number of Nodules from Baseline at Week 20: Per Protocol Population  
(Last Observation Carried Forward)**

| Lesion Type     | Accutane NF |         |          | Accutane |         |          | Ratio * | 95% CI **     |
|-----------------|-------------|---------|----------|----------|---------|----------|---------|---------------|
|                 | Baseline    | Week 20 | Change   | Baseline | Week 20 | Change   |         |               |
| Facial Nodules  |             | (N=251) |          |          | (N=241) |          |         |               |
| Mean            | 10.5        | 0.8     | -9.6     | 9.2      | 0.7     | -8.6     | 0.979   | 0.923 - 1.038 |
| SD              | 9.5         | 2.1     | 9.2      | 6.5      | 1.9     | 6.5      |         |               |
| Median          | 10.0        | 0.0     | -9.0     | 9.0      | 0.0     | -8.0     |         |               |
| Range           | 0 - 100     | 0 - 20  | -95 - 4  | 0 - 58   | 0 - 20  | -58 - 3  |         |               |
| Truncal Nodules |             | (N=251) |          |          | (N=241) |          |         |               |
| Mean            | 10.2        | 1.5     | -8.6     | 9.4      | 1.1     | -8.3     | 0.944   | 0.869 - 1.025 |
| SD              | 13.8        | 4.9     | 11.8     | 13.0     | 3.1     | 11.8     |         |               |
| Median          | 7.0         | 0.0     | -6.0     | 6.0      | 0.0     | -6.0     |         |               |
| Range           | 0 - 110     | 0 - 64  | -110 - 5 | 0 - 109  | 0 - 23  | -103 - 3 |         |               |
| Total Nodules   |             | (N=251) |          |          | (N=241) |          |         |               |
| Mean            | 20.6        | 2.4     | -18.3    | 18.7     | 1.8     | -16.9    | 0.954   | 0.899 - 1.011 |
| SD              | 18.4        | 5.7     | 16.1     | 13.1     | 4.0     | 12.2     |         |               |
| Median          | 15.0        | 0.0     | -14.0    | 14.0     | 0.0     | -13.0    |         |               |
| Range           | 10 - 200    | 0 - 66  | -184 - 6 | 10 - 111 | 0 - 28  | -105 - 4 |         |               |

\* Ratio is defined as lsmean change of Accutane NF/Accutane

\*\* 95% confidence interval for the ratio of lsmean change from baseline.

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## 2.2.4 Proportion of Patients Achieving at Least a 90% Reduction in Total Nodules

As Table 2 shows, equivalent proportions of patients achieved at least a 90% reduction from baseline at Week 20 (LOCF) in total nodules (70.9% in the Accutane NF group and 78.4% in the Accutane group). For the observed response rates in this study, the appropriate  $\delta$  value for evaluating clinical equivalence is 20%. The lower limit of the 95% confidence interval (-15.565%) is not less than  $-\delta$  (-20%) so that equivalence can be concluded from this analysis.

**Table 2 Patients Who Achieved at Least a 90% Reduction in the Total Number of Nodules from Baseline at Week 20: Per Protocol Population (Last Observation Carried Forward)**

| % Reduction   | Accutane NF<br>(N=251) |         | Accutane<br>(N=241) |         | Difference<br>(%) | CI              |
|---|------------------------|---------|---------------------|---------|-------------------|-----------------|
|   | N                      | %       | N                   | %       |                   |                 |
| < 90  | 73                     | ( 29.1) | 52                  | ( 21.6) |                   |                 |
| >= 90   | 178                    | ( 70.9) | 189                 | ( 78.4) | (-7.5)            | -15.565 - 0.551 |
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## 2.2.5 Need for Retreatment

- No retreatment was needed with either formulation of isotretinoin for the vast majority of patients (>80%) when evaluated 16 weeks post-therapy*

Both formulations showed a low rate of need for retreatment, in the investigators' judgement, when evaluated 16 weeks after completing the course of therapy (i.e., 20 weeks). The proportion of patients who did not require a second course of treatment was 174 of 213 (81.7%) in the Accutane NF group compared with 175 of 202 (86.6%) in the Accutane group. These data represent the 415 patients in the per protocol population who could be contacted at Week 36. These results are within the range of retreatment that one would expect in clinical practice with oral isotretinoin. It should be noted that this study was not designed to assess the need for retreatment, which should be considered over an 18-24 month post-treatment period.

## 2.3 Safety

- The adverse event profile observed for the Accutane NF group was similar to that of the Accutane group in the clinical trial: clinically relevant safety and tolerability advantages were observed for patients in the Accutane NF group and no new adverse events were reported*

Although a formal statistical safety analysis was not a primary goal of the clinical trial, a full safety evaluation was conducted. Statistical analyses for two key safety variables were

prospectively defined: 1) mucocutaneous adverse events (MAEs); and 2) marked clinical laboratory test abnormalities for lipids and liver transamination enzyme tests. A statistically significant difference in favor of the Accutane NF group was found in incidence and intensity of the five most common MAEs associated with oral isotretinoin therapy. Elevations in triglyceride and cholesterol levels were less in the Accutane NF group than in the Accutane group. Overall, the adverse event profile for both groups was consistent with what has been observed in clinical experience.

### **2.3.1 Overview of Clinical Adverse Events**

- *Most patients in both groups experienced adverse events, primarily mucocutaneous in nature, that were considered treatment-related*
- *The majority of adverse events in both groups were mild or moderate in intensity*

In the Accutane NF group, 296 of 300 patients reported a total of 1362 adverse events; in the Accutane group, 293 of 300 patients reported 1450 adverse events. Of the 602 patients randomized, two patients did not receive any treatment. Over 95% of all patients experienced adverse events that were considered probably related to study drug. Approximately 15% of all adverse events were unrelated to study drug.

The majority of adverse events (about 90%) were mild or moderate in intensity. There were no deaths during the study. Sixteen patients from each treatment group withdrew prematurely because of adverse events. Two patients in the Accutane NF group and four patients in the Accutane group experienced serious adverse events; however, only two of these serious adverse events required that the patient discontinue the study—one for pregnancy (Accutane NF group) and the other for appendicitis (Accutane group).

In both treatment groups, the most common adverse events were mucocutaneous: cheilitis, dry skin and other cutaneous conditions, epistaxis and nasal dryness. The incidences of the most frequently reported adverse events were slightly lower in the Accutane NF group compared with the Accutane group. With the exceptions of dry skin and headache, the incidences of these most frequently reported adverse events were slightly lower in the Accutane NF group compared with the Accutane group.

Adverse events in the “Psychiatric Disorders” body system were relatively uncommon (less than expected based on epidemiological predictions), but were reported in greater numbers in patients in the Accutane NF group (11 patients, 3.7%) compared with the Accutane group (1 patient, 0.3%). Section 2.3.4 will discuss these events in detail.

### **2.3.2 Mucocutaneous Adverse Events**

- *MAEs were fewer and less intense in Accutane NF-treated patients than in Accutane-treated patients*

As Table 3 shows, the spectrum of incidence and intensities of each of the five pre-specified MAEs (cheilitis or chapped lips, dry or irritated eyes, dry or peeling skin, dry or bleeding nose, and facial rash or erythema) is significantly different in favor of the Accutane NF group, who

experienced less intense MAEs at one or more time points during treatment. Cheilitis was the most common MAE and had the highest percentage of severe cases. At Week 2, the difference between treatment groups was statistically significant,  $p=0.0008$ . The other four MAEs clustered in intensity around the absent or mild categories; the differences were significant at several time points between Week 2 and Week 12. Thereafter, the difference between the formulations was not statistically significant.

The reduced intensities of the MAEs related to epistaxis and/or dry eyes are relevant for patient tolerability. Moderate and severe MAEs can reduce or affect daily activities. If taking Accutane NF results in fewer nose-bleeds and/or less need for eye-drops or removal of contact lenses, then patients may be more compliant with the treatment regimen. Therefore, because of the overall trend for fewer and less intense MAEs, Accutane NF will provide increased tolerability and convenience.

**Accutane NF (isotretinoin)  
Capsules**



**Table 3 Summary of Mucocutaneous Adverse Events Assessment: Intent-to-Treat (ITT) Population**

| Mucocutaneous Event            | N   | Absent   | Accutane NF Mild | Moderate N (%) | Severe  | N   | Absent   | Accutane Mild | Moderate N (%) | Severe  | P-Value * |
|--------------------------------|-----|----------|------------------|----------------|---------|-----|----------|---------------|----------------|---------|-----------|
| <b>Dry or Peeling Skin</b>     |     |          |                  |                |         |     |          |               |                |         |           |
| Baseline                       | 300 | 221 (74) | 69 (23)          | 9 (3)          | 1 (0)   | 300 | 224 (75) | 67 (22)       | 9 (3)          | 0 (0)   | 0.6979    |
| Week 2                         | 269 | 81 (30)  | 136 (51)         | 51 (19)        | 1 (0)   | 268 | 34 (13)  | 154 (57)      | 71 (26)        | 9 (3)   | 0.0000    |
| Week 4                         | 290 | 51 (18)  | 161 (56)         | 65 (22)        | 13 (4)  | 286 | 24 (8)   | 163 (57)      | 91 (32)        | 8 (3)   | 0.0094    |
| Week 8                         | 282 | 64 (23)  | 158 (56)         | 55 (20)        | 5 (2)   | 271 | 36 (13)  | 163 (60)      | 57 (21)        | 15 (6)  | 0.0024    |
| Week 12                        | 281 | 79 (28)  | 154 (55)         | 44 (16)        | 4 (1)   | 258 | 52 (20)  | 154 (60)      | 44 (17)        | 8 (3)   | 0.0353    |
| Week 16                        | 254 | 81 (32)  | 134 (53)         | 35 (14)        | 4 (2)   | 241 | 69 (29)  | 130 (54)      | 39 (16)        | 3 (1)   | 0.4280    |
| Week 20                        | 265 | 117 (44) | 116 (44)         | 28 (11)        | 4 (2)   | 255 | 101 (40) | 120 (47)      | 29 (11)        | 5 (2)   | 0.3238    |
| <b>Dry or Bleeding Nose</b>    |     |          |                  |                |         |     |          |               |                |         |           |
| Baseline                       | 300 | 290 (97) | 8 (3)            | 2 (1)          | 0 (0)   | 300 | 287 (96) | 9 (3)         | 4 (1)          | 0 (0)   | 0.4266    |
| Week 2                         | 269 | 198 (74) | 61 (23)          | 9 (3)          | 1 (0)   | 268 | 160 (60) | 82 (31)       | 22 (8)         | 4 (1)   | 0.0001    |
| Week 4                         | 290 | 178 (61) | 82 (28)          | 28 (10)        | 2 (1)   | 286 | 146 (51) | 101 (35)      | 36 (13)        | 3 (1)   | 0.0195    |
| Week 8                         | 282 | 174 (62) | 82 (29)          | 22 (8)         | 4 (1)   | 271 | 146 (54) | 79 (29)       | 43 (16)        | 3 (1)   | 0.0158    |
| Week 12                        | 281 | 189 (67) | 63 (22)          | 25 (9)         | 4 (1)   | 258 | 156 (60) | 80 (31)       | 18 (7)         | 4 (2)   | 0.3983    |
| Week 16                        | 254 | 174 (69) | 61 (24)          | 16 (6)         | 3 (1)   | 241 | 151 (63) | 72 (30)       | 16 (7)         | 2 (1)   | 0.3544    |
| Week 20                        | 265 | 194 (73) | 48 (18)          | 16 (6)         | 7 (3)   | 255 | 175 (69) | 59 (23)       | 19 (7)         | 2 (1)   | 0.7063    |
| <b>Dry or Irritated Eyes</b>   |     |          |                  |                |         |     |          |               |                |         |           |
| Baseline                       | 300 | 275 (92) | 23 (8)           | 2 (1)          | 0 (0)   | 300 | 276 (92) | 23 (8)        | 1 (0)          | 0 (0)   | 0.7845    |
| Week 2                         | 269 | 213 (79) | 44 (16)          | 10 (4)         | 2 (1)   | 268 | 180 (67) | 74 (28)       | 14 (5)         | 0 (0)   | 0.0146    |
| Week 4                         | 290 | 206 (71) | 64 (22)          | 16 (6)         | 4 (1)   | 286 | 179 (63) | 88 (31)       | 16 (6)         | 3 (1)   | 0.1476    |
| Week 8                         | 282 | 189 (67) | 75 (27)          | 16 (6)         | 2 (1)   | 271 | 153 (56) | 89 (33)       | 27 (10)        | 2 (1)   | 0.0086    |
| Week 12                        | 281 | 200 (71) | 59 (21)          | 21 (7)         | 1 (0)   | 258 | 154 (60) | 75 (29)       | 25 (10)        | 4 (2)   | 0.0066    |
| Week 16                        | 254 | 180 (71) | 55 (22)          | 16 (6)         | 3 (1)   | 241 | 150 (62) | 67 (28)       | 19 (8)         | 5 (2)   | 0.0550    |
| Week 20                        | 265 | 197 (74) | 54 (20)          | 11 (4)         | 3 (1)   | 255 | 172 (67) | 63 (25)       | 18 (7)         | 2 (1)   | 0.1010    |
| <b>Chapped Lips</b>            |     |          |                  |                |         |     |          |               |                |         |           |
| Baseline                       | 300 | 209 (70) | 78 (26)          | 12 (4)         | 1 (0)   | 300 | 223 (74) | 70 (23)       | 7 (2)          | 0 (0)   | 0.1101    |
| Week 2                         | 269 | 18 (7)   | 135 (50)         | 99 (37)        | 17 (6)  | 268 | 10 (4)   | 102 (38)      | 133 (50)       | 23 (9)  | 0.0008    |
| Week 4                         | 290 | 5 (2)    | 124 (43)         | 123 (42)       | 38 (13) | 286 | 5 (2)    | 114 (40)      | 129 (45)       | 38 (13) | 0.6118    |
| Week 8                         | 282 | 5 (2)    | 129 (46)         | 110 (39)       | 38 (13) | 271 | 7 (3)    | 113 (42)      | 115 (42)       | 36 (13) | 0.7200    |
| Week 12                        | 281 | 15 (5)   | 128 (46)         | 104 (37)       | 34 (12) | 258 | 9 (3)    | 118 (46)      | 99 (38)        | 32 (12) | 0.5596    |
| Week 16                        | 254 | 15 (6)   | 124 (49)         | 84 (33)        | 31 (12) | 241 | 11 (5)   | 110 (46)      | 89 (37)        | 31 (13) | 0.3502    |
| Week 20                        | 265 | 35 (13)  | 128 (48)         | 80 (30)        | 22 (8)  | 255 | 26 (10)  | 117 (46)      | 91 (36)        | 21 (8)  | 0.2298    |
| <b>Facial Rash or Erythema</b> |     |          |                  |                |         |     |          |               |                |         |           |
| Baseline                       | 300 | 258 (86) | 37 (12)          | 2 (1)          | 3 (1)   | 300 | 257 (86) | 34 (11)       | 7 (2)          | 2 (1)   | 0.7296    |
| Week 2                         | 269 | 201 (75) | 56 (21)          | 10 (4)         | 2 (1)   | 268 | 184 (69) | 67 (25)       | 17 (6)         | 0 (0)   | 0.1561    |
| Week 4                         | 290 | 215 (74) | 58 (20)          | 14 (5)         | 3 (1)   | 286 | 184 (64) | 81 (28)       | 20 (7)         | 1 (0)   | 0.0424    |
| Week 8                         | 282 | 218 (77) | 56 (20)          | 6 (2)          | 2 (1)   | 271 | 186 (69) | 73 (27)       | 11 (4)         | 1 (0)   | 0.0353    |
| Week 12                        | 281 | 225 (80) | 50 (18)          | 4 (1)          | 2 (1)   | 258 | 184 (71) | 64 (25)       | 10 (4)         | 0 (0)   | 0.0299    |
| Week 16                        | 254 | 200 (79) | 46 (18)          | 7 (3)          | 1 (0)   | 241 | 180 (75) | 53 (22)       | 7 (3)          | 1 (0)   | 0.3704    |
| Week 20                        | 265 | 216 (82) | 44 (17)          | 4 (2)          | 1 (0)   | 255 | 204 (80) | 39 (15)       | 11 (4)         | 1 (0)   | 0.3300    |

\* P-value taken from PROC CATMOD

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### 2.3.3 Laboratory Tests

- *Elevations in triglyceride and cholesterol levels were less in the Accutane NF group than in the Accutane group*

#### 2.3.3.1 Serum Triglyceride Levels

Serum triglyceride values increased by  $0.57 \pm 0.871$  mmol/L over baseline to  $1.73 \pm 1.002$  mmol/L at Week 20 in the Accutane NF group. In the Accutane group, triglycerides increased by  $0.99 \pm 1.441$  mmol/L over baseline to  $2.11 \pm 1.670$  mmol/L at Week 20. In terms of relative increase, serum triglyceride levels increased 49% over baseline for patients in the Accutane NF group and 88% for patients in the Accutane group.

A total of 48 patients (16.3%) treated with Accutane NF had instances of markedly elevated triglyceride levels compared with 75 patients (25.6%) treated with Accutane. This observation represents a significant difference between the formulations in favor of a trend towards better clinical safety for Accutane NF compared with Accutane. This difference is further corroborated by the finding that of the nine patients who withdrew prematurely from the clinical study because of elevated triglyceride levels, three were from the Accutane NF group and six were from the Accutane group.

#### 2.3.3.2 Cholesterol Levels

Total cholesterol values in the Accutane NF group increased by  $0.4 \pm 0.56$  mmol/L over baseline to  $4.6 \pm 0.96$  mmol/L at Week 20. In the Accutane group, cholesterol values increased by  $0.6 \pm 0.69$  mmol/L over baseline to  $4.8 \pm 1.02$  mmol/L at Week 20. In terms of relative increase, total cholesterol levels increased 9.5% over baseline for patients in the Accutane NF group and 14.3% for patients in the Accutane group.

There was only one marked abnormal cholesterol level reported which occurred in a patient in the Accutane group as a single, not last value.

### 2.3.4 Psychiatric Disorders

- *The greater number of psychiatric adverse events reported with Accutane NF is not indicative of increased risk. There is no evidence from the clinical trial of any increased risk of developing depression during oral isotretinoin treatment*

A Beck Depression Inventory (BDI-II) was recorded at baseline and at the end of treatment (Week 20) for each patient in the clinical trial [Beck et al., 1996]. In addition, at each visit, a four-item Mood/Depression Assessment Questionnaire was given to test for the onset of depressive symptoms and to determine whether a BDI-II should be administered. (The Beck Depression Inventory, Second Edition, is provided as Attachment 1 and the Mood/Depression Assessment Questionnaire as Attachment 2.) A BDI-II score of  $\geq 31$ , signifying severe depression, was a criterion for exclusion from enrollment in the trial; any patient who recorded such a score during the trial would have been immediately withdrawn from treatment and referred for psychiatric counseling.

Almost identical overall decreases in depression scores were observed in both treatment groups. The mean BDI-II scores at baseline were  $3.5 \pm 4.6$  (range 0-24) and  $3.6 \pm 4.5$  (range 0-29) for the Accutane NF and Accutane groups, respectively. The values at Week 20 decreased to  $1.7 \pm 3.1$  (range 0-21) and  $1.9 \pm 3.7$  (range 0-28) for the Accutane NF and Accutane groups, respectively. No patient had a score of  $\geq 31$  on the BDI-II. All BDI-II scores fell into the minimal, mild, or moderate categories.

Each screening tool, the Mood/Depression Assessment Questionnaire and the Beck Depression Inventory, detected equivalent numbers of patients with mood changes in each treatment group. Equal numbers of patients answered two or more questions positively on the Mood/Depression Assessment Questionnaire: 37 patients in the Accutane NF group on 45 occasions and 38 patients in the Accutane group on 48 occasions. Approximately equal numbers of patients from each treatment group had BDI-II scores that raised or lowered the grade by one or two units (three patients in the Accutane NF group and four patients in the Accutane group).

There were more self-reports of mood changes reported in the Accutane NF group; however, examination of these events reveals no difference in risk between the two treatment groups:

- The adverse events reported by the two groups had distinctly different characteristics. In the Accutane NF group, six patients (2.0%) reported episodes of depression, two patients (0.7%) reported mood swings, and one patient (0.3%) each reported panic reaction, anxiety, and mood alteration. One patient (0.3%) in the Accutane group reported a panic reaction.
- There is no detectable signal of increased risk for depression in either group: the incidence of depression in both groups (2.0% and 0.0%, respectively) is less than the prevalence in the general population.
- None of the reported adverse events represents true clinical depression, as determined by an independent review of the patient narratives by a psychiatrist.

Thus, in light of these considerations, the disparity between the treatment groups is not likely to have clinical significance, and rather than representing a cluster with underlying similarity of symptoms, these patients comprise a set of unrelated individual reports.

## **2.4 Dosage Regimen**

Four pharmacokinetic studies assessed the food effect on bioavailability; established the bioequivalence of clinical and registration lots of Accutane NF; and established the dose proportionality of three registration lots of Accutane NF.

### **2.4.1 Principal Findings**

- *0.4 mg/kg once daily dosing of Accutane NF fasted yields comparable exposures to the lowest labeled dose of Accutane fed (0.5 mg/kg twice daily dosing)*
- *Unlike Accutane, Accutane NF given fasted or fed yields comparable exposures*

- *This decreased variability of exposure reduces the risk of suboptimal efficacy or safety from inappropriate administration conditions*
- *The higher variability of Accutane resulting from a food effect makes it unfeasible to administer Accutane once daily with the same efficacy and safety of Accutane NF*
- *Modeling supports a dose range for Accutane NF; giving Accutane NF at doses higher than 0.4 mg/kg would produce a similar pharmacokinetic exposure to the most commonly used dose of Accutane, 1.0 mg/kg, given twice daily with food*
- *Because of their important pharmacokinetic differences, the potential confusion between Accutane NF and Accutane must be avoided through risk management to ensure the safe and efficacious use of oral isotretinoin*

## **2.4.2 Determining Exposure for Accutane NF and Accutane**

### **2.4.2.1 Methodology**

Data from the fed/fasted pharmacokinetic study (Protocol NR15805) were used to investigate differences in exposure for different dosage regimens of Accutane NF and Accutane under fasting or fed conditions. Since the pharmacokinetics of isotretinoin are linear within the range of concentrations investigated, classical pharmacokinetic superpositioning principles were used to simulate the steady-state exposures to isotretinoin. The plasma concentration curves were simulated to obtain the steady-state maximum plasma concentration ( $C_{\max}$ ) and the area under the plasma concentration curve over 24 hours ( $AUC_{0-24}$ ).

Note: Throughout this simulation, all doses were calculated for a 70 kg subject assuming that any dose strengths needed were available.

### **2.4.2.2 Results**

- *0.4 mg/kg once daily dosing of Accutane NF fasted yields comparable exposures to the lowest labeled dose of Accutane fed (0.5 mg/kg twice daily dosing)*

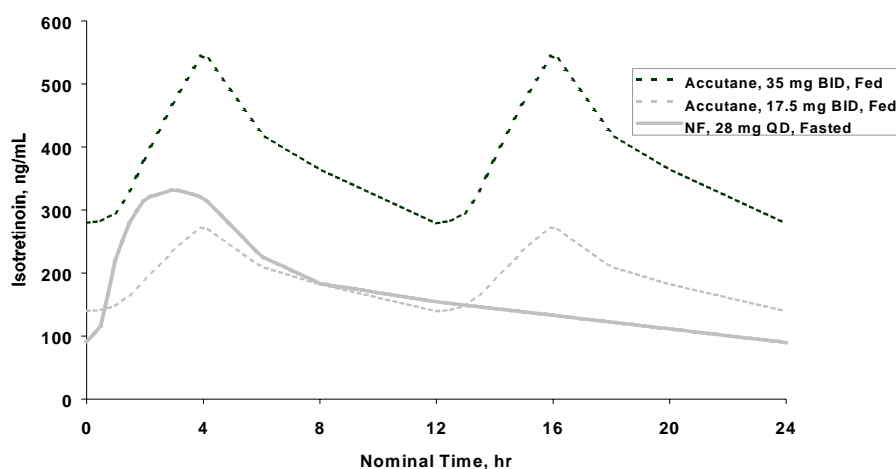
Based on the results of the safety and efficacy study (Protocol NR15645), comparable efficacy and overall safety results were obtained for 0.4 mg/kg of Accutane NF and 1.0 mg/kg of Accutane in the clinical trial. Given this positive comparison, the pharmacokinetic exposure following the administration of these formulations has also been compared. In addition, the exposure following the administration of 0.5 mg/kg of Accutane, the minimum dose specified in the label, has been simulated and compared with 0.4 mg/kg of Accutane NF. Table 4 presents the relative steady-state exposure ( $C_{\max}$  and  $AUC_{0-24}$ ) to isotretinoin following the administration of these three dosage regimens. The corresponding simulated mean plasma concentration-time profiles for each dosage regimen are presented in Figure 1.

**Table 4**      **Relative Steady-State Exposure to Isotretinoin Following the Administration of Accutane (1.0 mg/kg and 0.5 mg/kg) and Accutane NF (0.4 mg/kg)**

| PARAMETER                     | Accutane, Fed<br>(1.0 mg/kg, divided)<br>35 mg BID | Accutane, Fed<br>(0.5 mg/kg, divided)<br>17.5 mg BID | Accutane NF, Fasted<br>(0.4 mg/kg, once daily)<br>28 mg QD |
|-------------------------------|--|--|--|
| C <sub>max</sub> (ng/mL)      | 544.6  | 272.3  | 331.6  |
| AUC <sub>0-24</sub> (ng*h/mL) | 9209.4   | 4604.7   | 4161.4   |

All doses are based on a 70 kg subject

**Figure 1**      **Relative Steady-State Exposure to Isotretinoin Following the Administration of Accutane (1.0 mg/kg and 0.5 mg/kg) and Accutane NF (0.4 mg/kg)**



As shown in Table 4 and Figure 1, the exposure following the administration of a 28 mg dose (0.4 mg/kg) of Accutane NF once daily under fasting conditions is very similar to the exposure following the administration of a 35 mg divided dose (0.5 mg/kg) of Accutane under fed conditions.

### 2.4.3 Effect of Food on Exposure

- *Unlike Accutane, Accutane NF given fasted or fed yields comparable exposures*
- *This decreased variability of exposure reduces the risk of suboptimal efficacy or safety from inappropriate administration conditions*

A large food effect of Accutane has been documented in the literature and is reflected in the Accutane label which requires Accutane to be administered with food [Colburn et al., 1983]. When Accutane is administered with food there is approximately a factor of 2 increase in the extent of absorption when compared with Accutane administered under fasting conditions. This large food effect can have a significant impact on the daily exposure to isotretinoin if patients do not take their Accutane dose with food.

The Accutane NF formulation was specifically designed to minimize the food effect so that patients could easily take their medication with or without food, thus minimizing exposure differences. The extent of absorption when Accutane NF is administered with food is approximately 30% greater than when it is administered without food. The safety and efficacy study (Protocol NR15645) was designed with Accutane NF being administered under fasting conditions, knowing that administration with food would result in only a slight increase in isotretinoin exposure.

Table 5 and Table 6 and Figure 2 and Figure 3 provide the exposure and plasma concentration curves for a 70 mg (1.0 mg/kg) divided dose of Accutane and a 35 mg (0.5 mg/kg) divided dose of Accutane, compared with a 28 mg (0.4 mg/kg) once daily dose of Accutane NF under fed and fasted conditions.

**Table 5**      **Relative Steady-State Exposure to Isotretinoin Following the Administration of Accutane (1.0 mg/kg) and Accutane NF (0.4 mg/kg) Under Fed and Fasted Conditions**

| PARAMETER                     | Accutane, Fed<br>(1.0 mg/kg,<br>divided)<br>35 mg BID | Accutane, Fasted<br>(1.0 mg/kg,<br>divided)<br>35 mg BID | Accutane NF, Fed<br>(0.4 mg/kg, once<br>daily)<br>28 mg QD | Accutane NF, Fasted<br>(0.4 mg/kg, once<br>daily)<br>28 mg QD |
|-------------------------------|---|--|--|---|
| C <sub>max</sub> (ng/mL)      | 544.6   | 202.1  | 423.4  | 331.6   |
| AUC <sub>0-24</sub> (ng*h/mL) | 9209.4  | 3655.4   | 5460.5   | 4161.4  |

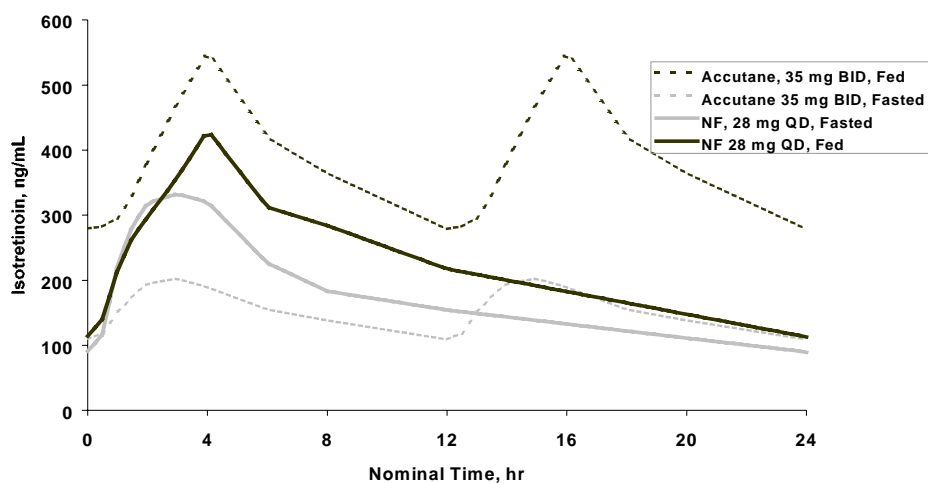
All doses are based on a 70 kg subject

**Table 6**      **Relative Steady-State Exposure to Isotretinoin Following the Administration of Accutane (0.5 mg/kg) and Accutane NF (0.4 mg/kg) Under Fed and Fasted Conditions**

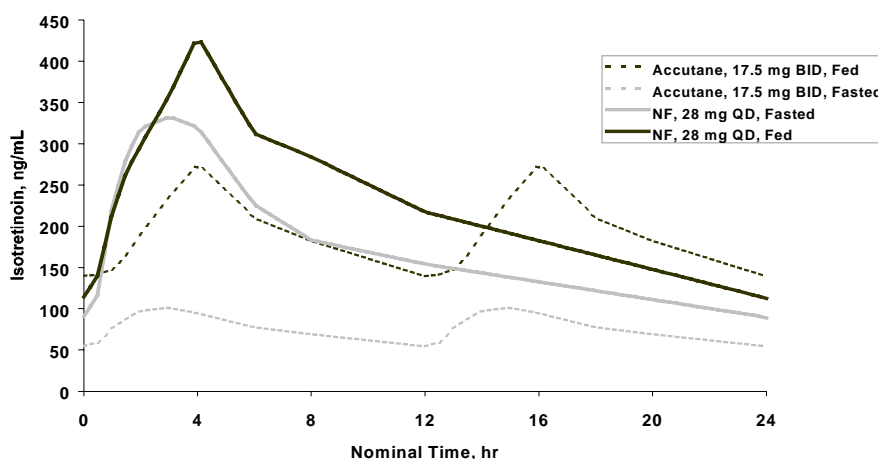
| PARAMETER              | Accutane, Fed<br>(0.5 mg/kg,<br>divided)<br>17.5 mg BID | Accutane, Fasted<br>(0.5 mg/kg,<br>divided)<br>17.5 mg BID | Accutane NF, Fed<br>(0.4 mg/kg, once<br>daily)<br>28 mg QD | Accutane NF, Fasted<br>(0.4 mg/kg, once<br>daily)<br>28 mg QD |
|------------------------|---|--|--|---|
| $C_{max}$ (ng/mL)      | 272.3   | 101.1  | 423.4  | 331.6   |
| $AUC_{0-24}$ (ng*h/mL) | 4604.7  | 1827.7   | 5460.5   | 4161.4  |

All doses are based on a 70 kg subject

**Figure 2**      **Relative Steady-State Exposure to Isotretinoin Following the Administration of Accutane (1.0 mg/kg) and Accutane NF (0.4 mg/kg) Under Fed and Fasted Conditions**



**Figure 3**      **Relative Steady-State Exposure to Isotretinoin Following the Administration of Accutane (0.5 mg/kg) and Accutane NF (0.4 mg/kg) Under Fed and Fasted Conditions**



As seen in Table 5 and Table 6 and Figure 2 and Figure 3, the exposures ( $C_{max}$  and  $AUC_{0-24}$ ) for Accutane NF under both fed and fasting conditions are all within the range of Accutane exposure as described in its label, where the minimum recommended dose is 0.5 mg/kg, and as studied within the clinical efficacy and safety trial described previously. Figure 2 and Figure 3 also show that there is a significant decrease in exposure when Accutane is not administered with food (e.g., if the patient is not compliant with the requirement for concomitant administration with food). The plasma concentration profiles and the exposures of Accutane 0.5-1.0 mg/kg under fasting conditions are lower than Accutane NF 0.4 mg/kg under fasting conditions. In fact, the efficacy of such a dosing regimen (35 or 70 mg divided dose of Accutane under fasting conditions) has never been investigated in an adequate well-controlled clinical study. Given that the exposure for 35–70 mg (0.5-1.0 mg/kg) of Accutane under fasting conditions has a lower exposure than even the minimal dose of Accutane (0.5 mg/kg divided) under fed conditions, a dose of 0.5-1.0 mg/kg of Accutane under fasting conditions is unlikely to be efficacious.

The ability to take Accutane NF under either fed or fasting conditions reduces the risk of inappropriate administration. A patient who does not take Accutane consistently with food is more likely to have a decrease in response, possibly resulting in a relapse and additional courses of therapy, than a patient taking Accutane NF with or without food.

## 2.4.4 Modeling of Alternate Treatment Regimens

- *The higher variability of Accutane resulting from a food effect makes it unfeasible to administer Accutane once daily with the same efficacy and safety of Accutane NF*
- *Modeling supports a dose range for Accutane NF; giving Accutane NF at doses higher than 0.4 mg/kg would produce a similar pharmacokinetic exposure to the most commonly used dose of Accutane, 1.0 mg/kg, given twice daily with food*

### 2.4.4.1 Impact of Once Daily Administration of Accutane

The clinical trial (NR15645) demonstrated the equivalent efficacy of 0.4 mg/kg of Accutane NF administered once daily under fasting conditions and 1.0 mg/kg of Accutane administered as a divided dose under fed conditions. The question naturally arises whether Accutane administered once a day would be equally efficacious. Although an adequate well-controlled clinical study has never been performed to address this issue, the pharmacokinetic plasma profile and the exposures of Accutane and Accutane NF for different dosage regimens suggests otherwise.

Table 7, Table 8, and Table 9 and Figure 4, Figure 5, and Figure 6 represent the various dosing scenarios that were simulated to address this issue.

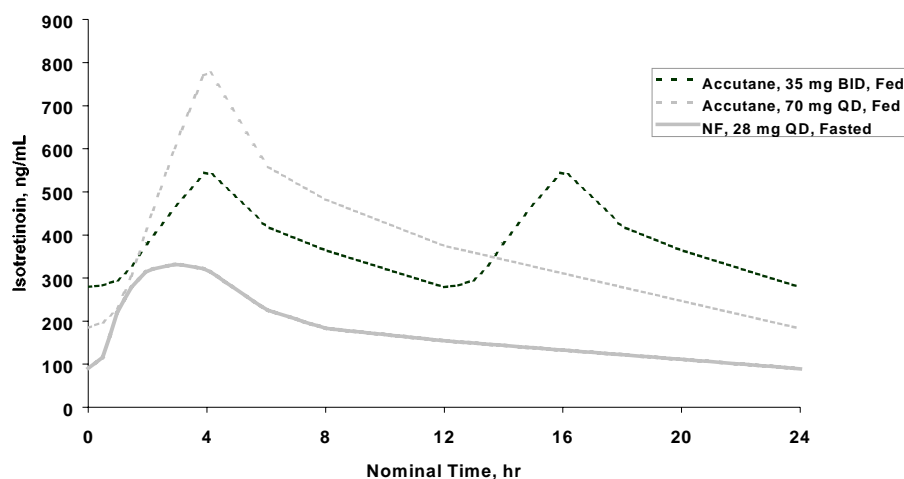
- 1) A 70 mg once daily dose of Accutane (Table 7, Figure 4) with food
- 2) A 30 mg once daily dose of Accutane administered with food which will result in a  $C_{\max}$  exposure equal to the proven efficacious dose of 28 mg of Accutane NF administered once daily without food (Table 8, Figure 5)
- 3) A 83 mg once daily dose of Accutane administered without food which will result in a  $C_{\max}$  exposure equal to the proven efficacious dose of 28 mg of Accutane NF administered once daily without food (Table 9, Figure 6)

**Table 7**      **Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg) Given as Divided Doses and as a Single Dose Compared with Accutane NF (0.4 mg/kg)**

| PARAMETER              | Accutane, Fed<br>1.0 mg/kg, divided<br>(35 mg BID) | Accutane, Fed<br>1.0 mg/kg, once daily<br>(70 mg QD) | Accutane NF, Fasted<br>0.4 mg/kg, once daily<br>(28 mg QD) |
|------------------------|--|--|--|
| $C_{\max}$ (ng/mL)     | 544.6  | 776.7  | 331.6  |
| $AUC_{0-24}$ (ng*h/mL) | 9209.4   | 9209.8   | 4161.4   |

All doses are based on a 70 kg subject

**Figure 4**      **Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg) Given as Divided Doses and as a Single Dose Compared with Accutane NF (0.4 mg/kg)**

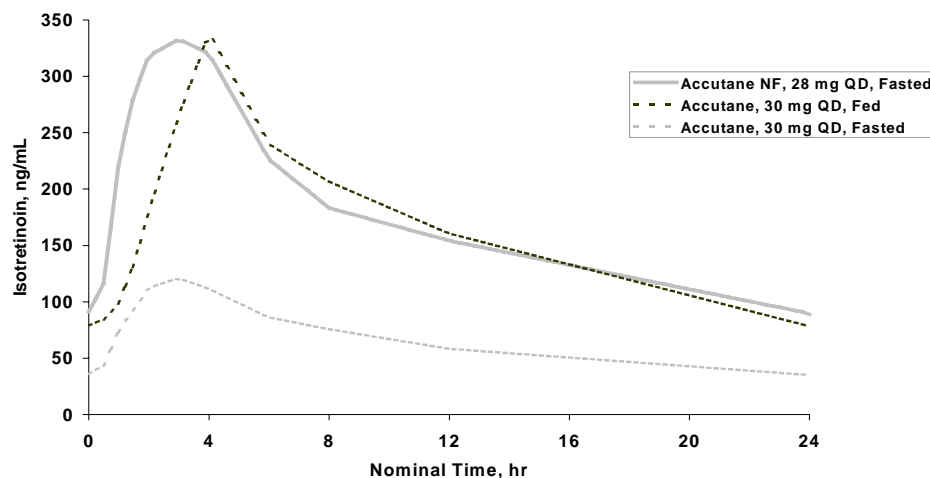


**Table 8**      **Comparable Steady-State Exposure to Isotretinoin Following Single Dose Administration of Accutane Under Fed Conditions Relative to Accutane NF Administered Under Fasted Conditions**

| PARAMETER                     | Accutane NF, Fasted<br>0.4 mg/kg, once daily<br>(28 mg QD) | Accutane, Fed<br>0.44 mg/kg, once daily<br>(30 mg QD) | Accutane, Fasted<br>0.44 mg/kg, once daily<br>(30 mg QD) |
|-------------------------------|--|---|--|
| C <sub>max</sub> (ng/mL)      | 331.6  | 332.8   | 120.3  |
| AUC <sub>0-24</sub> (ng*h/mL) | 4161.4   | 3946.3  | 1566.5   |

All doses are based on a 70 kg subject

**Figure 5**      **Comparable Steady-State Exposure to Isotretinoin Following Single Dose Administration of Accutane Under Fed Conditions Relative to Accutane NF Administered Under Fasted Conditions**

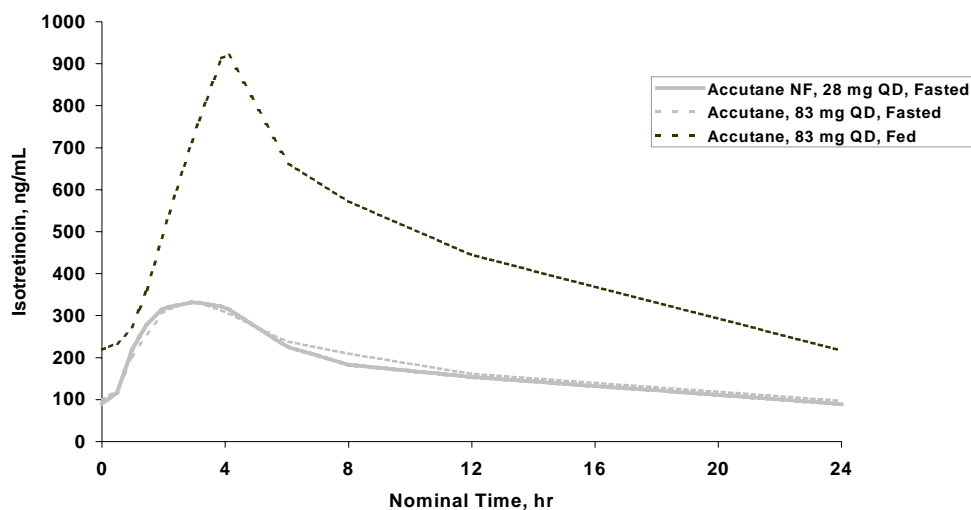


**Table 9**      **Comparable Steady-State Exposure to Isotretinoin Following Single Dose Administration of Accutane Under Fasted Conditions Relative to Accutane NF Administered Under Fasted Conditions**

| PARAMETER              | Accutane NF, Fasted<br>(0.4 mg/kg), once daily<br>28 mg QD | Accutane, Fasted<br>(1.2 mg/kg), once daily<br>83 mg QD | Accutane, Fed<br>(1.2 mg/kg), once daily<br>83 mg QD |
|------------------------|--|---|--|
| $C_{max}$ (ng/mL)      | 331.6  | 332.8   | 921.0  |
| $AUC_{0-24}$ (ng*h/mL) | 4161.4   | 4334.0  | 10920.2  |

All doses are based on a 70 kg subject

**Figure 6**      **Comparable Steady-State Exposure to Isotretinoin Following Single Dose Administration of Accutane Under Fasted Conditions Relative to Accutane NF Administered Under Fasted Conditions**



These results show that a 70 mg single daily dose of Accutane administered with food will result in a much higher  $C_{max}$  than either the 70 mg divided dose of Accutane administered with food or the 28 mg dose of Accutane NF administered under fasting conditions (Table 7, Figure 4). This higher  $C_{max}$  would be anticipated to increase the safety risk.

#### **2.4.4.2 Matching Accutane Fed to Accutane NF Under Fasting Conditions**

The natural next is then to define a dose of Accutane under fed conditions that would match the 28 mg dose of Accutane NF that was proven to be efficacious. These results (Table 8, Figure 5) show that a dose (30 mg) can easily be defined, but the risk of taking the dose without food would result in exposures well below any values that have ever been studied in an adequate well-controlled clinical study. The lower exposures could result in decreased efficacy.

Table 9 and Figure 6 represent the same thought process if one were to define a dose of Accutane administered once daily but without food. A dose of 83 mg of Accutane under fasting conditions administered once daily would match the  $C_{max}$  of a 28 mg dose of Accutane NF administered once daily without food. However, if the dose of Accutane was accidentally administered *with* food, the resulting exposure would be greater than 70 mg divided or 70 mg as a single dose. The  $C_{max}$  would be closer to that predicted for a 2.0 mg/kg divided dose of Accutane administered with food. The higher exposure from accidentally taking the 83 mg with food would increase the probability of having more and/or more intense adverse events.

Administering Accutane once daily, therefore, increases the probability of suboptimal safety or efficacy if patients are not compliant. These increased risks do not support once daily administration of Accutane.

#### **2.4.4.3 Matching Accutane NF $C_{max}$ to Accutane Administered as a Divided Dose**

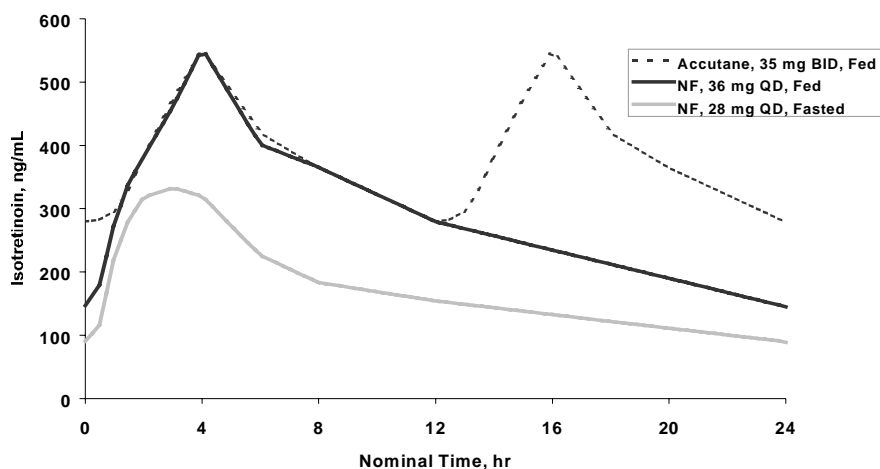
To complete the investigation, a calculation was done to determine the dose of Accutane NF needed to have the same  $C_{max}$  as 70 mg of Accutane administered as a divided dose under fed conditions (Table 10, Figure 7). The results show that 36 mg of Accutane NF administered once daily under fed conditions (or 0.5 mg/kg) would result in a  $C_{max}$  equal to that of a 70 mg divided dose of Accutane administered with food. This dose would also result in  $C_{min}$  and AUC values between those values of the equally efficacious doses of the 70 mg of Accutane given as divided doses and the 28 mg once daily dose of Accutane NF (Figure 7). Under fasting conditions, the  $C_{max}$ ,  $C_{min}$ , and AUC for this 36 mg dose would still be within the above range. Performing the reciprocal analysis with Accutane NF administered under fasting conditions (Table 11, Figure 8) results in a dose of 46 mg of Accutane NF (or 0.66 mg/kg). This dose, however, administered under fed conditions would result in a higher exposure than a 70 mg divided dose of Accutane.

**Table 10 Comparable Steady-State Exposure to Isotretinoin Following Single Dose Administration of Accutane NF Under Fed Conditions Relative to Accutane Administered Under Fed Conditions**

| PARAMETER                     | Accutane, Fed<br>(1.0 mg/kg), divided<br>35 mg BID | Accutane NF, Fed<br>(0.51 mg/kg), once daily<br>36 mg QD | Accutane NF, Fasted<br>(0.4 mg/kg), once daily<br>28 mg QD |
|-------------------------------|--|--|--|
| $C_{max}$ (ng/mL)             | 544.6  | 544.4  | 331.6  |
| AUC <sub>0-24</sub> (ng*h/mL) | 9209.4   | 7020.6   | 4161.4   |

All doses are based on a 70 kg subject

**Figure 7**      **Comparable Steady-State Exposure to Isotretinoin Following Single Dose Administration of Accutane NF Under Fed Conditions Relative to Accutane Administered Under Fed Conditions**

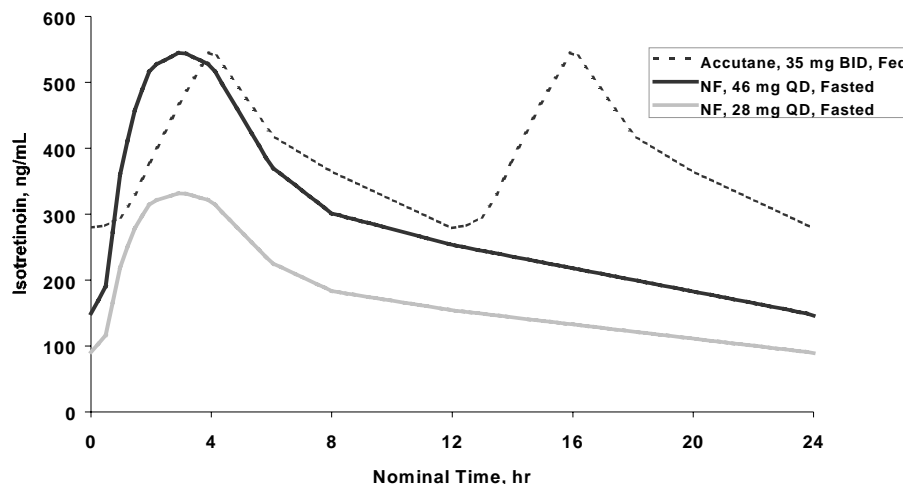


**Table 11**      **Comparable Steady-State Exposure to Isotretinoin Following Single Dose Administration of Accutane NF Under Fasted Conditions Relative to Accutane Administered Under Fed Conditions**

| PARAMETER                     | Accutane, Fed<br>(1.0 mg/kg), divided<br>35 mg BID | Accutane NF, Fasted<br>(0.66 mg/kg), once daily<br>46 mg QD | Accutane NF, Fasted<br>(0.4 mg/kg), once daily<br>28 mg QD |
|-------------------------------|--|---|--|
| C <sub>max</sub> (ng/mL)      | 544.6  | 544.8   | 331.6  |
| AUC <sub>0-24</sub> (ng*h/mL) | 9209.4   | 6836.6  | 4161.4   |

All doses are based on a 70 kg subject

**Figure 8**      **Comparable Steady-State Exposure to Isotretinoin Following Single Dose Administration of Accutane NF Under Fasted Conditions Relative to Accutane Administered Under Fed Conditions**



#### 2.4.5 Risks from the Potential Confusion between Accutane NF and Accutane

- *Because of their important pharmacokinetic differences, the potential confusion between Accutane NF and Accutane must be avoided through risk management to ensure the safe and efficacious use of oral isotretinoin*

The two oral isotretinoin products (Accutane NF and Accutane) could be confused by the prescriber, the pharmacist, and/or the patient. Two scenarios are presented below to model the consequences of product confusion.

##### Scenario 1: Confusing Administration Conditions

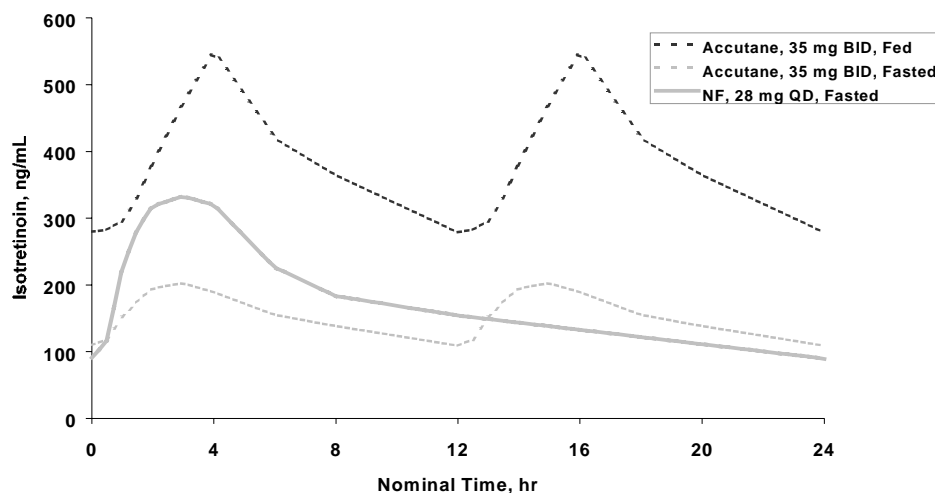
As has been discussed in the previous sections, Accutane is to be administered with food. Administering Accutane without food increases the risk of suboptimal efficacy (Table 12, Figure 9). The exposure of 70 mg of Accutane in a divided dose administered without food is even less than 28 mg of Accutane NF fasted and 70 mg of Accutane in a divided dose with food. In contrast, administering Accutane NF with or without food does not significantly alter patient exposure (Table 13, Figure 10) and should not alter the efficacy or safety of the drug.

**Table 12** Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg) Compared with Accutane NF (0.4 mg/kg) Administered Under Fasted Conditions

| PARAMETER              | Accutane, Fed<br>(1.0 mg/kg), divided<br>35 mg BID | Accutane, Fasted<br>(1.0 mg/kg), divided<br>35 mg BID | Accutane NF, Fasted<br>(0.4 mg/kg), once daily<br>28 mg QD |
|------------------------|--|---|--|
| $C_{\max}$ (ng/mL)     | 544.6  | 202.1   | 331.6  |
| $AUC_{0-24}$ (ng*h/mL) | 9209.4   | 3655.4  | 4161.4   |

All doses are based on a 70 kg subject

**Figure 9** Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg) Compared with Accutane NF (0.4 mg/kg) Administered Under Fasted Conditions

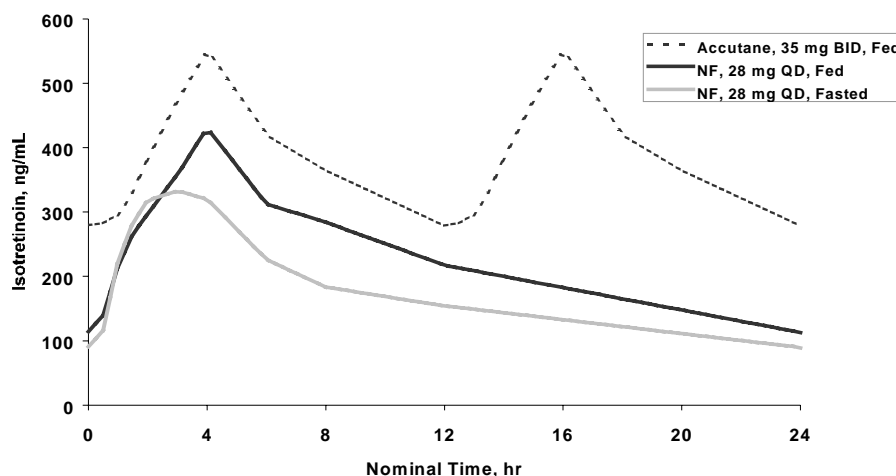


**Table 13**      **Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg) Administered Under Fed Conditions Compared with Accutane NF (0.4 mg/kg)**

| PARAMETER                     | Accutane, Fed<br>(1.0 mg/kg), divided<br>35mg BID | Accutane NF, Fasted<br>(0.4 mg/kg), once daily<br>28 mg QD | Accutane NF, Fed<br>(0.4 mg/kg), once daily<br>28 mg QD |
|-------------------------------|---|--|---|
| C <sub>max</sub> (ng/mL)      | 544.6   | 331.6  | 423.4   |
| AUC <sub>0-24</sub> (ng*h/mL) | 9209.4  | 4161.4   | 5460.5  |

All doses are based on a 70 kg subject

**Figure 10**      **Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg) Administered Under Fed Conditions Compared with Accutane NF (0.4 mg/kg)**



#### Scenario 2: Confusing Administration Intervals

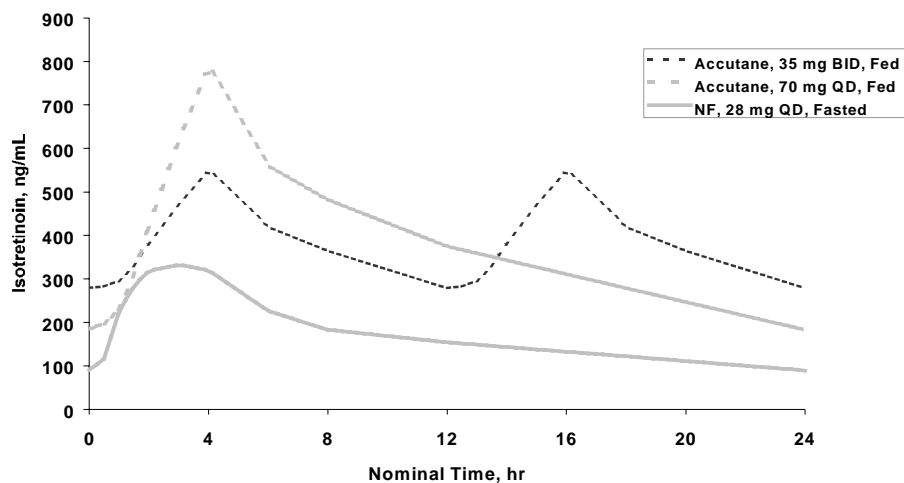
The potential confusion of taking Accutane once a day or Accutane NF BID exists if both drugs are on the market. The relevant pharmacokinetic information is provided in Table 14 and Figure 11. By mistakenly administering the 70 mg of Accutane once a day rather than in divided doses (as indicated in the label), a significantly higher C<sub>max</sub> would result with the possibility of safety consequences. Table 15 and Figure 12 illustrate the consequences of mistakenly taking 28 mg of Accutane NF in a divided dose. The exposure would be slightly less than that from the divided dose of 35 mg of Accutane (0.5 mg/kg) administered with food, the lowest dose recommended within the Accutane label.

**Table 14** Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg) Given as Divided Doses and as a Single Dose Compared with Accutane NF (0.4 mg/kg)

| PARAMETER                     | Accutane, Fed<br>(1.0 mg/kg), divided<br>35 mg BID | Accutane, Fed<br>(1.0 mg/kg), once daily<br>70 mg QD | Accutane NF, Fasted<br>(0.4 mg/kg), once daily<br>28 mg QD |
|-------------------------------|--|--|--|
| C <sub>max</sub> (ng/mL)      | 544.6  | 776.7  | 331.6  |
| AUC <sub>0-24</sub> (ng*h/mL) | 9209.4   | 9209.8   | 4161.4   |

All doses are based on a 70 kg subject

**Figure 11** Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg) Given as Divided Doses and as a Single Dose Compared with Accutane NF (0.4 mg/kg)

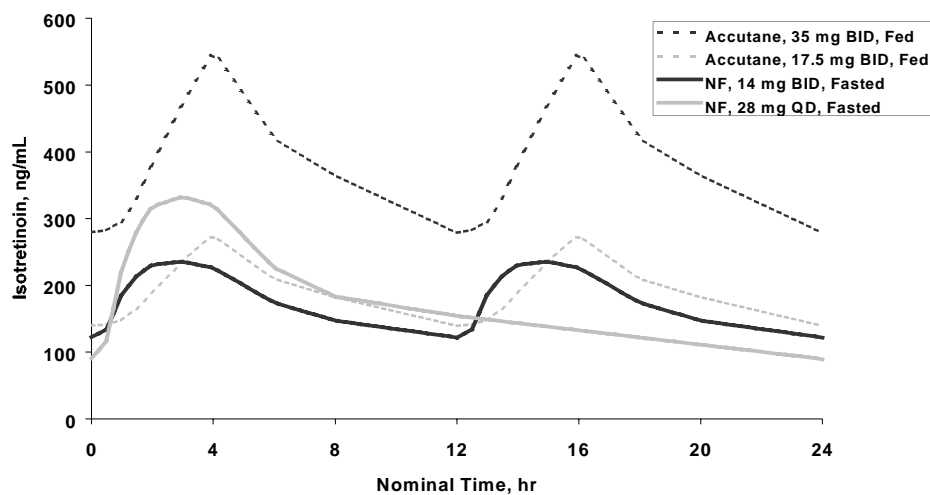


**Table 15**      **Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg and 0.5 mg/kg) Compared with Accutane NF (0.4 mg/kg)**

| PARAMETER              | Accutane, Fed<br>(1.0 mg/kg), divided<br>35 mg BID | Accutane NF,<br>Fasted<br>(0.4 mg/kg),<br>once daily<br>28 mg QD | Accutane NF,<br>Fasted<br>(0.4 mg/kg),<br>divided<br>14 mg BID | Accutane, Fed<br>(0.5 mg/kg),<br>divided<br>17.5 mg BID |
|------------------------|--|--|--|---|
| $C_{max}$ (ng/mL)      | 544.6  | 331.6  | 235.2  | 272.3   |
| $AUC_{0-24}$ (ng*h/mL) | 9209.4   | 4161.4   | 4161.8   | 4604.7  |

All doses are based on a 70 kg subject

**Figure 12**      **Relative Steady-State Exposure to Isotretinoin Following Administration of Accutane (1.0 mg/kg and 0.5 mg/kg) Compared with Accutane NF (0.4 mg/kg)**



### Conclusion

Although one hopes that confusion in prescribing, dispensing, and/or administering these two formulations does not occur, the purpose of this section was to describe the drug exposures that would result from two possible scenarios. The simulations show that Accutane NF administered BID or with food will probably not alter the efficacy or safety of Accutane NF. However, Accutane administered QD or without food could compromise the therapy.

## 2.5 Accutane NF NDA Conclusions

- *Micronization of isotretinoin leads to administration independent of food, reduced variability, and increased bioavailability*
- *The new micronized formulation achieved clinically equivalent efficacy to the current marketed Accutane, clinically relevant safety and tolerability advantages were demonstrated and no new safety concerns were identified*

## 3. RISK MANAGEMENT OF THE NEW FORMULATION OF ISOTRETINOIN

- *The clinical impact of having two formulations on the market concurrently creates efficacy and safety concerns; plans are in place to manage this potential confusion*

### 3.1 Risk Assessment

Because of the differences in the pharmacokinetic properties of Accutane NF and Accutane, it is necessary to ensure that any possible confusion of the two drugs is avoided. Micronization of isotretinoin allows Accutane NF to produce comparable exposures when taken with or without food. In contrast, the exposures would differ by a factor of 2 for the current marketed Accutane, leading to the risk of suboptimal efficacy or increased adverse events. Possible risks of confusion include the following:

- Inappropriate dosing of Accutane NF and Accutane
- Concurrent administration of Accutane NF and Accutane
- Confusion about capsule strengths in the prescription
- Uncertainty about bioavailability and actual exposure of the drugs
- Misunderstanding about once daily administration without food for Accutane NF and twice daily with food for Accutane
- Potential for inappropriate substitution of the products at the pharmacy

### 3.2 Risk Management

To properly inform prescribers, pharmacists, and patients, Accutane NF will exhibit new packaging, capsule appearance, and package insert instructions. More specifically, Accutane NF will be differentiated from Accutane by the following marketing features:

#### 1. Unique packaging

- Pouches versus prescription packs
- Packaging shape and color

#### 2. Capsule appearance

- Contrasting capsule color schemes
- Different identification marks on the capsules

#### 3. A distinctive and unique brand name for Accutane NF

- Trade name submitted to the FDA in July 2000

A trade name was proposed to maintain recognition of the drug (i.e., Accutane), while also stressing importance differences. The new name was designed to avoid confusion in writing and filling prescriptions. Because the new name begins with a different letter, the products should be physically separated on the pharmacy shelf.

### **3.3 Educational Interventions**

Upon approval of the NDA, information about the new formulation will be distributed through prescriber and pharmacy education programs.

- Professional representatives will double the frequency of their visits to allow them to individually inform and train prescribing dermatologists in the safe and efficacious use of the product.
- All prescribers and pharmacists will receive an information sheet that emphasizes differences in the dosage regimen, capsule sizes, colors and identification markings of the capsules, and packaging components of the two products. A kg/weight dose chart will also be included.
- CME and CEU courses will be offered to all health care professionals.
- Prescribers will be advised not to switch the therapy of patients already taking Accutane to the new formulation.
- Specific instructions will be given by the provider to patients not to mix Accutane NF and Accutane capsules, and not to share medication with family members or friends.

## **4. REFERENCES**

Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory, Second Edition, San Antonio, TX, The Psychological Corporation, 1996.

Colburn WA, Gibson DM, Wiens RE, et al. Food increases the bioavailability of isotretinoin. J Clin Pharmacol 1983; 23: 534-539.

Fleiss JL. Statistical methods for rates and proportions. New York, John Wiley & Sons, 1981, pp. 29-30.



# Beck Depression Inventory

Baseline

V 0477

CRTN: \_\_\_\_\_ CRF number: \_\_\_\_\_

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patient initials: \_\_\_\_\_



Date: \_\_\_\_\_

Name: \_\_\_\_\_ Marital Status: \_\_\_\_\_ Age: \_\_\_\_\_ Sex: \_\_\_\_\_

Occupation: \_\_\_\_\_ Education: \_\_\_\_\_

**Instructions:** This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

## 1. Sadness

- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

## 2. Pessimism

- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

## 3. Past Failure

- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

## 4. Loss of Pleasure

- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

## 5. Guilty Feelings

- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

## 6. Punishment Feelings

- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

## 7. Self-Dislike

- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

## 8. Self-Criticalness

- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

## 9. Suicidal Thoughts or Wishes

- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

## 10. Crying

- 0 I don't cry anymore than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.



# Beck Depression Inventory

Baseline

V 0477

CRTN: \_\_\_\_\_ CRF number: \_\_\_\_\_

Page 15

patient initials: \_\_\_\_\_

## 11. Agitation

- 0 I am no more restless or wound up than usual.
- 1 I feel more restless or wound up than usual.
- 2 I am so restless or agitated that it's hard to stay still.
- 3 I am so restless or agitated that I have to keep moving or doing something.

## 12. Loss of Interest

- 0 I have not lost interest in other people or activities.
- 1 I am less interested in other people or things than before.
- 2 I have lost most of my interest in other people or things.
- 3 It's hard to get interested in anything.

## 13. Indecisiveness

- 0 I make decisions about as well as ever.
- 1 I find it more difficult to make decisions than usual.
- 2 I have much greater difficulty in making decisions than I used to.
- 3 I have trouble making any decisions.

## 14. Worthlessness

- 0 I do not feel I am worthless.
- 1 I don't consider myself as worthwhile and useful as I used to.
- 2 I feel more worthless as compared to other people.
- 3 I feel utterly worthless.

## 15. Loss of Energy

- 0 I have as much energy as ever.
- 1 I have less energy than I used to have.
- 2 I don't have enough energy to do very much.
- 3 I don't have enough energy to do anything.

## 16. Changes in Sleeping Pattern

- 0 I have not experienced any change in my sleeping pattern.
- 1a I sleep somewhat more than usual.
- 1b I sleep somewhat less than usual.
- 2a I sleep a lot more than usual.
- 2b I sleep a lot less than usual.
- 3a I sleep most of the day.
- 3b I wake up 1-2 hours early and can't get back to sleep.

## 17. Irritability

- 0 I am no more irritable than usual.
- 1 I am more irritable than usual.
- 2 I am much more irritable than usual.
- 3 I am irritable all the time.

## 18. Changes in Appetite

- 0 I have not experienced any change in my appetite.
- 1a My appetite is somewhat less than usual.
- 1b My appetite is somewhat greater than usual.
- 2a My appetite is much less than before.
- 2b My appetite is much greater than usual.
- 3a I have no appetite at all.
- 3b I crave food all the time.

## 19. Concentration Difficulty

- 0 I can concentrate as well as ever.
- 1 I can't concentrate as well as usual.
- 2 It's hard to keep my mind on anything for very long.
- 3 I find I can't concentrate on anything.

## 20. Tiredness or Fatigue

- 0 I am no more tired or fatigued than usual.
- 1 I get more tired or fatigued more easily than usual.
- 2 I am too tired or fatigued to do a lot of the things I used to do.
- 3 I am too tired or fatigued to do most of the things I used to do.

## 21. Loss of Interest in Sex

- 0 I have not noticed any recent change in my interest in sex.
- 1 I am less interested in sex than I used to be.
- 2 I am much less interested in sex now.
- 3 I have lost interest in sex completely.

Subtotal Page 2

Subtotal Page 1

Total Score

NR15645

3 4 5 6 7 8 9 10 11 12 A B C D E



V 0477

**Mood/depression  
questionnaire**

CRTN: \_\_\_\_\_ CRF number: \_\_\_\_\_

Page 20

patient initials: \_\_\_\_\_

**Week 2****Mood/Depression Assessment Questionnaire**

1. Since your last visit have you felt depressed, sad or blue much of the time?

yes ☐no ☐

2. Since your last visit have you often felt helpless about the future?

yes ☐no ☐

3. Since your last visit have you had little interest or pleasure in doing things?

yes ☐no ☐

4. Since your last visit have you had trouble sleeping many nights?

yes ☐no ☐

Are two (2) or more of the above questions marked YES while undergoing treatment in this protocol?

yes ☐ → *complete a Beck Depression Inventory. If score is 30 or less, patient may continue in the study. If score is  $\geq 31$ , patient will need to complete all final assessments and be dropped from the study. The investigator may recommend that the patient be referred for a professional psychiatric assessment.*

no ☐